# SUPPLEMENTARY TABLES

*CPT: pharmacometrics & systems pharmacology*

## Prediction of gastric pH-mediated drug exposure using physiologically based pharmacokinetic modeling: A case study of itraconazole

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**Table S1.** Clinical data in healthy subjects used in PBPK modeling and simulation

| | **Legacy Study 1**[a] (Unpublished data; NCT02328443) | **Legacy Study 2** (Lange, D et al.[1]) | **Current Prospective Study** |
|---|---|---|---|
| PK data used in PBPK model | Development | Validation | Validation |
| ITR/OH-ITR PK profile | Y/N | Y/Y | Y/Y |
| Subjects with PK data | Healthy Korean (N=10)<br>• Age, years: 21-30<br>• Male:Female, %: 100:0 | Healthy individuals[b] (N=30)<br>• Age, years: 20-42<br>• Male:Female, %: 100:0 | Healthy Korean (N=12)<br>• Age, years: 21-43<br>• Male:Female, %: 100:0 |
| Dosing regimen | 200 mg twice q12h<br>Capsule | 200 mg single<br>Capsule | 200 mg single<br>Capsule |
| Gastric condition | Normal gastric acidity<br>• Fasted | Normal gastric acidity<br>• Fasted | Normal gastric acidity<br>• Fasted |
| | - | - | Normal gastric acidity<br>• Fed |
| | - | Induced gastric hypoacidity<br>• Fasted + Ranitidine | Induced gastric hypoacidity<br>• Fasted + Esomeprazole |

PBPK, physiologically based pharmacokinetic; ITR, itraconazole; OH-ITR, hydroxy-itraconazole; Form., formulation; PK, pharmacokinetic

[a] In Legacy Study 1 conducted in our working group, plasma concentrations for itraconazole were quantified only in 10 subjects among 24 subjects at timepoints of 1, 1.17, 1.33, 1.5, 1.75, 2, 3, 4, 5, 7, 9, 13, 25, and 49 hours after the second itraconazole dosing with 12-hour dosing interval. Refer to the CYP3A-inhibition phase of Study A in reference [2] for detailed description.

[b] The subjects' ethnicity in Legacy Study 2 was not specified in the published report.

**Table S2.** PBPK model input parameters for itraconazole

| Parameters | Value | Reference |
|---|---|---|
| **Physicochemical properties** | | |
| Molecular weight (g/moL) | 705.6 | Simcyp Library V20 |
| Log $P_{o:w}$ | 4.47 | Simcyp Library V20 |
| Compound type | Monoprotic base | |
| $pK_a$ | 3.7 | Sporanox cap FDA label, 2019 |
| Blood:Plasma ratio (B/P) | 0.58 | Simcyp Library V20 |
| Fraction unbound in plasma ($f_{u,p}$) | 0.02 | Simcyp Library V20 |
| **Absorption - Advanced Dissolution Absorption Metabolism (ADAM) model** | | |
| Permeability; $P_{eff,man}$ ($10^{-4}$ cm/s) | 7.74 | Predicted in Simcyp |
| MechPeff model; $P_{trans,0}$ ($10^{-6}$ cm/s) | 1724.13 | Predicted in Simcyp |
| ***Diffusion Layer Model (DLM)*** | | |
| Aqueous intrinsic solubility (mg/mL) | 1.00E-05 | [3] |
| Intrinsic solubility scalar ($So_{scalar}$) | 612.00 | [4] |
| Solubility factor (SF) | 227314.29 | [3] |
| DLM scalar | 0.35 | Estimated in Simcyp[a] |
| Particle density (g/mL) | 1.2 | Simcyp default |
| Particle size distribution | Monodispersed | Simcyp default |
| Particle radius (µm) | 26.37 | Estimated in Simcyp[a] |
| Particle $h_{eff}$ prediction | Hintz–Johnson method | Simcyp default |
| $LogK_{m:w,unionized}$ | 5.51 (fasted), 5.00 (fed) | Estimated in SIVA |
| $LogK_{m:w,ionized}$ | 5.79 (fasted), 6.08 (fed) | Estimated in SIVA |
| Critical supersaturation ratio (CSR) | 44.97 | [5] |
| Precipitation rate constant (PRC) ($h^{-1}$) | 2.11 | [5] |
| Monomer diffusion coeff ($10^{-4}$ $cm^2/s$) | 3.17 | Predicted in Simcyp |
| Micelle diffusion coeff ($10^{-4}$ $cm^2/s$) | 0.78 | Simcyp default |
| **Distribution - Minimal PBPK** | | |

| | | |
|---|---|---|
| $V_{ss}$ (L/kg) | 3.9 | [6,7] |
| $V_{sac}$ (L/kg) | 1.6 | [8] |
| $k_{in}/k_{out}$ ($h^{-1}$) | 0.22/0.06 | [8] |
| **Elimination** | | |
| CYP3A4 $V_{max}$ (pmol/min/pmol) | 0.065 | Simcyp Library V20 |
| CYP3A4 $K_m$ (µm) | 0.0039 | Simcyp Library V20 |
| CYP1A2 $CL_{int}$ (µL/min/pmol) | 1 | Simcyp Library V20 |
| **Interaction** | | |
| CYP3A4 $K_i$(µm) | 0.0013 | Simcyp Library V20 |
| CYP3A4 $f_{u,mic}$ | 1 | Simcyp Library V20 |

PBPK, physiologically based pharmacokinetic; $P_{o:w}$, octanol:buffer partition coefficient; $P_{eff,man}$, human jejunum effective permeability; $P_{trans,0}$, intrinsic transcellular permeability; $h_{eff}$, effective diffusion layer thickness; $K_{m:w}$, bile salt micelle to water partition coefficient; $V_{ss}$, steady state volume of distribution; $V_{sac}$, apparent volume of a single adjusting compartment (SAC); $k_{in}$, rate constant from systemic compartment to SAC; $k_{out}$, rate constant from SAC to systemic compartment; $V_{max}$, maximum rate of metabolism; $K_m$, Michaelis-Menten constant; $CL_{int}$, *in vitro* intrinsic clearance; $K_i$, concentration of inhibitor that supports half maximal inhibition; $f_{u,mic}$, fraction of unbound drug in the *in vitro* microsomal incubation

[a] Clinical data from Legacy Study 1 was used for parameter estimation in Simcyp®.

**Table S3.** PBPK model input parameters for hydroxy-itraconazole

| Parameters | Value | Reference |
|---|---|---|
| **Physicochemical properties** | | |
| Molecular weight (g/moL) | 721.7 | Simcyp Library V20 |
| Log $P_{o:w}$ | 4.47 | Simcyp Library V20 |
| Compound type | Monoprotic base | |
| $pK_a$ | 4.28 | Simcyp Library V20 |
| Blood:Plasma ratio (B/P) | 0.58 | Simcyp Library V20 |
| Fraction unbound in plasma ($f_{u,p}$) | 0.016 | Simcyp Library V20 |
| **Absorption – First-order absorption model** | | |
| Fraction unbound in the gut ($f_{u,gut}$) | 0.016 | Simcyp Library V20 |
| **Distribution - Minimal PBPK** | | |
| $V_{ss}$ (L/kg) | 4.72 | [9] |
| $V_{sac}$ (L/kg) | 2.50 | [9] |
| $k_{in}/k_{out}$ (1/h) | 0.005/0 | [9] |
| **Elimination** | | |
| CYP3A4 $V_{max}$ (pmol/min/pmol) | 0.13 | Simcyp Library V20 |
| CYP3A4 $K_m$ (µm) | 0.027 | Simcyp Library V20 |
| **Interaction** | | |
| CYP3A4 $K_i$ (µm) | 0.0023 | Simcyp Library V20 |
| CYP3A4 $fu_{mic}$ | 1 | Simcyp Library V20 |

PBPK, physiologically based pharmacokinetic; $P_{o:w}$, octanol:buffer partition coefficient; $V_{ss}$, steady state volume of distribution; $V_{sac}$, apparent volume of a single adjusting compartment (SAC); $k_{in}$, rate constant from systemic compartment to SAC; $k_{out}$, rate constant from SAC to systemic compartment; $V_{max}$, maximum rate of metabolism; $K_m$, Michaelis-Menten constant; $K_i$, concentration of inhibitor that supports half maximal inhibition; $f_{u,mic}$, fraction of unbound drug in the *in vitro* microsomal incubation

**Table S4.** Trial designs used in PBPK model validation and application

| Trial | Reference | Description | Design | Dosing regimen | Population file used[a] |
|---|---|---|---|---|---|
| 1 | Current Prospective Study | **Model validation**<br>: Evaluation of predictability at fasted state under normal gastric acidity | • No. of trials: 10<br>• No. of subjects: 12<br>• Age: 21-43 years<br>• % of females: 0 | 200 mg single (fasted) | Healthy volunteers<br>• Fasted gastric pH<br>: 1.9 (18.4%) |
| 2 | Current Prospective Study | **Model validation**<br>: Evaluation of predictability at fed state under normal gastric acidity | • No. of trials: 10<br>• No. of subjects: 12<br>• Age: 21-43 years<br>• % of females: 0 | 200 mg single (fed) | Healthy volunteers<br>• Fed gastric pH<br>: 4.9 (22.0%) |
| 3 | Current Prospective Study | **Model validation**<br>: Evaluation of predictability at fasted state under induced gastric hypoacidity | • No. of trials: 10<br>• No. of subjects: 12<br>• Age: 21-43 years<br>• % of females: 0 | 200 mg single (fasted) | Healthy volunteers<br>• Fasted gastric pH<br>: 5.0 (38.3%) |
| 4 | Legacy Study 2 | **Model validation**<br>: Evaluation of predictability at fasted state under normal gastric acidity | • No. of trials: 10<br>• No. of subjects: 30<br>• Age: 20-42 years<br>• % of females: 0 | 200 mg single (fasted) | Healthy volunteers<br>• Fasted gastric pH<br>: 1.9 (18.4%) |
| 5 | Legacy Study 2 | **Model validation**<br>: Evaluation of predictability at fasted state under induced gastric hypoacidity | • No. of trials: 10<br>• No. of subjects: 30<br>• Age: 20-42 years<br>• % of females: 0 | 200 mg single (fasted) | Healthy volunteers<br>• Fasted gastric pH<br>: 5.0 (38.3%) |
| 6 | - | **Model application**<br>: Prediction of itraconazole exposure at fasted state under achlorhydria | • No. of trials: 10<br>• No. of subjects: 12<br>• Age: 21-43 years<br>• % of females: 0 | 200 mg single (fasted) | Healthy volunteers<br>• Fasted gastric pH<br>: 5.7 (8.9%) |
| 7 | - | **Model application**<br>: Prediction of itraconazole exposure at fed state under achlorhydria | • No. of trials: 10<br>• No. of subjects: 12<br>• Age: 21-43 years<br>• % of females: 0 | 200 mg single (fed) | Healthy volunteers<br>• Fed gastric pH<br>: 6.4 (11.5%) |

PBPK, physiologically based pharmacokinetic

[a] Based on itraconazole pharmacokinetics is not significantly different between Caucasian and Korean,[1, 10-12] we used 'healthy volunteers' population file for simulation.

**Table S5.** Summary of PBPK model refinement process

| Step | Description | Data used in PBPK model refinement | Parameter[a] | Value | |
|---|---|---|---|---|---|
| 1 | **Model 1 to Model 2**<br>: Parameter estimation for DLM scalar and particle radius in Simcyp® based on the evaluation results of predictability for itraconazole exposure at fasted state under normal gastric acidity observed in Legacy Study 1 | Legacy Study 1 clinical data | DLM scalar | Model 1 | 1 |
| | | | | Model 2 | 0.35 |
| | | | Particle radius (μM) | Model 1 | 10 |
| | | | | Model 2 | 26.37 |
| 2 | **Model 2 to Model 3**<br>: Application of the $K_{m:w}$ values estimated separately for fed and fasted states in Simcyp *In Vitro* data Analysis toolkit based on the evaluation results of predictability for gastric pH-mediated itraconazole exposure observed in Legacy Study 2 | *in vitro* biorelevant solubility data | $LogK_{m:w,unionized}$ | Model 2 | 5.13 |
| | | | | Model 3 | 5.51 (fasted), 5.00 (fed) |
| | | | $LogK_{m:w,ionized}$ | Model 2 | 5.79 |
| | | | | Model 3 | 5.79 (fasted), 6.08 (fed) |

PBPK, physiologically based pharmacokinetic; DLM, diffusion layer model; $K_{m:w}$, bile salt micelle to water partition coefficient

[a] Parameters not specified in Table S5 were not optimized or changed during PBPK model refinement process.

**Table S6.** Pharmacokinetic profiles in Current Prospective Study: Pharmacokinetic parameters of itraconazole and hydroxy-itraconazole following a single oral administration of itraconazole 200 mg alone or with esomeprazole 40 mg in fasted condition, or alone in fed condition

| | **ITR alone (Fasted) (N=12)** | **ITR + ESO (Fasted) (N=12)[a]** | | **ITR alone (Fed) (N=12)** | |
|---|---|---|---|---|---|
| | **Parameter** | **Parameter** | **GMR[b] (90% CI)** | **Parameter** | **GMR[c] (90% CI)** |
| **Itraconazole** | | | | | |
| $T_{max}$ (h) | 2.00 [2.00-3.00] | 3.00 [2.00-5.00] | - | 5.58 [4.00-8.00] | - |
| $C_{max}$ (µg/L) | 222.35 (54.29) | 188.34 (77.21) | 0.85 (0.60-1.20) | 219.28 (81.08) | 0.99 (0.69-1.40) |
| $AUC_{last}$ (h*µg/L) | 2030.34 (65.43) | 1773.33 (114.97) | 0.87 (0.58-1.31) | 2313.49 (109.90) | 1.14 (0.76-1.71) |
| $AUC_{inf}$ (h*µg/L) | 2563.22 (56.47) | 2178.04 (105.84) | 0.85 (0.59-1.22) | 2793.01 (98.57) | 1.09 (0.76-1.56) |
| $t_{1/2}$ (h) | 19.59 (26.35) | 18.01 (51.67) | - | 16.27 (66.58) | - |
| **Hydroxy-itraconazole** | | | | | |
| $T_{max}$ (h) | 3.50 [2.00-5.00] | 4.00 [2.00-8.00] | - | 6.06 [5.00-12.00] | - |
| $C_{max}$ (µg/L) | 249.62 (43.90) | 195.08 (40.76) | 0.78 (0.59-1.04) | 205.49 (42.73) | 0.82 (0.62-1.10) |
| $AUC_{last}$ (h*µg/L) | 3170.42 (66.84) | 2620.56 (91.42) | 0.83 (0.58-1.18) | 3392.68 (92.31) | 1.07 (0.75-1.53) |
| $AUC_{inf}$ (h*µg/L) | 3753.71 (60.40) | 3100.71 (86.73) | 0.83 (0.57-1.20) | 4013.90 (91.59) | 1.05 (0.72-1.54) |
| $t_{1/2}$ (h) | 11.54 (21.64) | 10.87 (33.52) | - | 10.27 (37.63) | - |
| Metabolic ratio[d] | 1.56 (14.20) | 1.48 (18.70) | - | 1.47 (24.76) | - |

Data are expressed as geometric mean (geometric coefficient of variation%), except for $T_{max}$, which are expressed as median [range].

ITR, itraconazole; ESO, esomeprazole; GMR, geometric mean ratio; CI, confidence interval; $T_{max}$, time to reach to maximum plasma concentration; $C_{max}$, maximum plasma concentration; $AUC_{last}$, area under the concentration-time curve (AUC) from 0 to last measurable time point; $AUC_{inf}$, AUC from 0 to infinity; $t_{1/2}$, half-life

[a] Number of subjects for $AUC_{inf}$ and $t_{1/2}$ of hydroxy-itraconazole was 11.

[b] GMR indicates ‘ITR + ESO (Fasted)’ to ‘ITR alone (Fasted)’.

[c] GMR indicates ‘ITR alone (Fed)’ to ‘ITR alone (Fasted)’.

[d] Ratio of $AUC_{last}$ of hydroxy-itraconazole to $AUC_{last}$ of itraconazole

**Table S7.** Predicted and observed time to reach to maximum plasma concentration ($T_{max}$) of itraconazole and hydroxy-itraconazole following a single oral administration of itraconazole 200 mg under normal gastric acidity or pharmacologically induced gastric hypoacidity

| Condition | Gastric pH | $T_{max}$ (h) | |
|---|---|---|---|
| | | Pred. | Obs. |
| **Itraconazole** | | | |
| ***Normal gastric acidity*** | | | |
| Fasted[(1)] | 1.9 | 1.92 [1.30-4.05] | 2.00 [2.00-3.00] |
| Fasted[(2)] | 1.9 | 2.02 ± 0.50 | 3.07 ± 0.83 |
| Fed[(1)] | 4.9 | 3.75 [2.20-7.20] | 5.58 [4.00-8.00] |
| ***Gastric hypoacidity*** | | | |
| Fasted + ESO[(1)] | 5.0 | 3.07 [1.65-5.50] | 3.00 [2.00-5.00] |
| Fasted + RAN[(2)] | 5.0 | 3.14 ± 0.84 | 3.60 ± 0.86 |
| **Hydroxy-itraconazole** | | | |
| ***Normal gastric acidity*** | | | |
| Fasted[(1)] | 1.9 | 5.30 [2.25-11.20] | 3.50 [2.00-5.00] |
| Fasted[(2)] | 1.9 | 5.68 ± 2.01 | 3.67 ± 0.66 |
| Fed[(1)] | 4.9 | 7.49 [4.20-13.35] | 6.06 [5.00-12.00] |
| ***Gastric hypoacidity*** | | | |
| Fasted + ESO[(1)] | 5.0 | 4.88 [2.40-9.70] | 4.00 [2.00-8.00] |
| Fasted + RAN[(2)] | 5.0 | 5.31 ± 1.67 | 4.13 ± 0.82 |

(1) and (2) refer to Current Prospective Study and Legacy Study 2, respectively.

$T_{max}$ is expressed as median [range] for (1) and arithmetic mean ± standard deviation for (2).

$T_{max}$, time to reach to maximum plasma concentration; ESO, esomeprazole; RAN, ranitidine

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